Verification of the Newly Proposed T Category (Seventh Edition of the Tumor, Node, and Metastasis Classification) from a Clinicopathological Viewpoint in Non-small Cell Lung Cancer—Special Reference to Tumor Size

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Introduction: This study first verified the T classification, which is the major point of the revision regarding the seventh Tumor, Node, and Metastasis classification, from a viewpoint of the clinicopathological findings at the primary tumor site in non-small cell lung cancer.

Methods: The medical records of 1393 patients with non-small cell lung cancer who underwent a complete resection at this hospital from 1974 to 2003 were thoroughly reviewed for pathologic findings and survival.

Results: According to greatest dimension of the primary tumors, the 5-year postoperative survival was 77.8% for T1a (≤2 cm), 63.3% for T1b (≤3 cm), 46.4% for T2a (≤5 cm), 38.8% for T2b (<7 cm), and 21.4% for T3 (>7 cm). The differences among those new T categories were all statistically significant. The incidence of lymphatic permeation within the primary tumor was 17.2% for T1b and 29.8% for T2a (T1b versus T2a, $p < 0.05$). The incidence of vascular invasion within the primary tumor was 24.9% for T1b, 35.3% for T2a, and 54.2% for T2b (T1b versus T2a and T2a versus T2b, $p < 0.05$). On the other hand, the incidence of pleural invasion of the primary tumor was 18.1% for T1a, 29.4% for T1b, 49.3% for T2a, 47.3% for T2b, and 87.5% for T3 (T1a versus T1b, T1b versus T2a, T2b versus T3, $p < 0.05$). Significant differences were observed among the newly revised T subsets in at least one incidence of lymphatic, vascular, or pleural invasion.

Conclusion: The new T classification, which is based mainly on the tumor size, is therefore considered to be appropriate for the pathologic findings of the primary tumor.

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Primary lung cancer is one of the most common malignancies in the world. It has been the leading cause of cancer death in Japan since 1998 and is still increasing in both prevalence and mortality. Despite recent progress in both radiotherapy and chemotherapy, a surgical resection remains the first choice of treatment for stages I to IIIA non-small cell lung cancer (NSCLC). However, the surgical results for patients with locally advanced stages (II or IIIA) are not satisfactory, even if a complete resection can be performed, and the 5-year survival rate is less than 50%.[1,2] Various effective modalities of the treatment are now warranted to improve the prognosis.

The tumor, node, and metastasis (TNM) staging system is useful for both the clinical assessment of tumor progression and the determination of treatment modality in various kinds of malignancy. In the forthcoming seventh edition of the TNM classification, a revision with respect to lung cancer has been proposed by the International Association for the Study of Lung Cancer.[3–6] The major revision is the T category, which makes an especially strict division by detailed cut points of tumor size such as 2, 3, 5, and 7 cm.[4] The proposed T revision has been determined and validated based on the overall survival data from a large international database.

In addition to conventional TNM staging including pleural invasion, pathologic evaluation of intratumoral vessel invasion (both blood vessels and lymphatic vessels) has been used as an indicator of tumor invasiveness in surgically resected NSCLC.[7] In fact, several studies have shown that the intratumoral vessel invasion is a significant prognostic factor, especially for pathologic stage I disease.[8–13]

This study first verified the T classification, which was the major point of revision regarding the newly proposed TNM classification, from a viewpoint of the clinicopathological findings at the primary tumor site, including microscopic vessel invasion and pleural invasion.

PATIENTS AND METHODS

Patients

The medical records of 1393 patients with primary NSCLC who underwent a complete resection in Kyushu University Hospital from 1974 to 2003 were thoroughly reviewed for pathologic diagnosis (histologic types and disease stage) and survival. This study was approved by the Kyushu University Institutional Review Board for Clinical Research.

The patients ranged in age from 23 to 87 years with a mean of 64.4 and included 939 men and 454 women. The histologic types were adenocarcinoma in 848 patients and nonadenocarcinoma in 545 patients. The stage of all the patients was pathologically defined according to the present international staging system previously revised in 1997.[1,14] Despite the performance of a systematic hilar-mediastinal lymph node dissection, the resection was regarded as complete if all the macroscopic tumors had been removed without any microscopically residual tumors at the surgical margin. The extent of the pulmonary resection was a pneumonectomy in 135 patients (9.7%), a lobectomy in 1172 patients (84.1%), a segmentectomy in 31 patients (2.2%), and a wedge resection in 55 patients (3.9%). Systematic hilar-mediastinal lymph node dissection was performed in 1032 patients (73.7%). Perioperative adjuvant treatment was not routinely performed during the entire period. From February 1993 to January 1995, 42 patients were enrolled into a clinical trial for the postoperative adjuvant chemotherapy, and 22 patients received combination chemotherapy of cisplatin plus oral tegafur and uracil.

A survival analysis was performed using the data of all the patients. A clinicopathological analysis was performed using the data of 621 patients that underwent a resection from 1990 to 2003, in whom the histopathological assessment of intratumoral vessel invasion was available in addition to that of pleural invasion. Written informed consent for the comprehensive use of histopathologic analyses was obtained from each patient.

Follow-Up of Postoperative Patients

A routine check-up with a physical examination, blood cell counts, serum chemistry, serum tumor markers including carcinoembryonic antigen and cytokeratin fragment 19, and chest x-rays were performed on an outpatient basis four times a year for the first 3 years, and thereafter twice annually. Since 1983, computed tomography and bone scans were performed twice a year for the first 3 years, and thereafter at least annually. Systemic chemotherapy and/or radiation were administered when a relapse was diagnosed, if it was feasible.

Histopathologic Evaluation

Formalin-fixed and paraffin-embedded surgical specimens were routinely used for the histopathological diagnosis at the department of pathology in Kyushu University Hospital. In addition to hematoxylin-eosin staining, Elastica van Gieson staining was applied for the evaluation of visceral pleural invasion and intratumoral vessel invasion. Pleural invasion was defined to extend beyond the elastic pleural layer. Both vascular invasion and lymphatic permeation indicated tumor cells identifiable in the vessel lumen in the maximal cut-surface specimen of the primary tumor. The identification of blood vessels was dependent on the presence of either elastic tissue around the vessels or erythrocytes in the lumen.

Statistics

For the analyses of the overall survival, each patient's time period began on the date of surgery and ended on the date of death or the last date of follow-up. The univariate survival analyses were estimated by the Kaplan-Meier test, and the differences among the groups were analyzed by the log-rank test. Comparisons of the clinicopathological variables among the T categories depending on tumor sizes were performed using Fisher's exact test. A two-sided $p < 0.05$ was considered to be statistically significant.

RESULTS

According to greatest dimension of the primary tumors with any pathologic node (pN) status, the 5-year postoperative survival was 77.8% for T1a (≤2 cm; $n = 298$), 63.3% for T1b (>2–≤3 cm; $n = 344$), 46.4% for T2a (>3–≤5 cm; $n = 485$), 38.8% for T2b (>5–≤7 cm; $n = 180$), and 21.4% for T3 (>7 cm; $n = 86$). The differences among those new T categories were all statistically significant (Figure 1). Except for 168 cases with a pN1 status and 314 cases with a pN2 status, the 5-year postoperative survival in the 911 cases of only pN0 status was 83.9% for T1a ($n = 246$), 74.6% for T1b ($n = 237$), 59.5% for T2a ($n = 283$), 53.5% for T2b ($n = 95$), and 30.8% for T3 ($n = 50$). Except for the difference between T2a and T2b, the differences among the T categories were also statistically significant (Figure 2).

Table 1 shows the correlation between the new T categories (greatest dimension of primary tumor) and the incidence of intratumoral vessel invasion or pleural invasion regarding the 621 patients from 1990 to 2003. The incidence of lymphatic permeation within the primary tumor was 12.5% for T1a, 17.2% for T1b, 29.8% for T2a, 35.4% for T2b, and

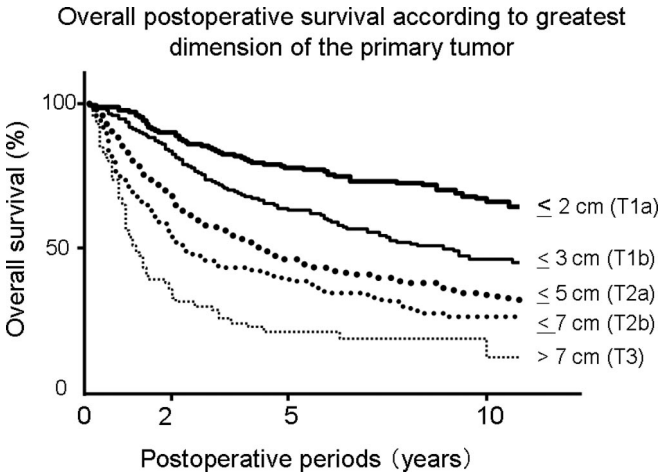

FIGURE 1. T1a ($n = 298$) versus T1b ($n = 344$), $p < 0.001$; T1b versus T2a ($n = 485$), $p < 0.001$; T2a versus T2b (n = 180), $p = 0.012$; and T2b versus T3 (n = 86), $p < 0.002$.

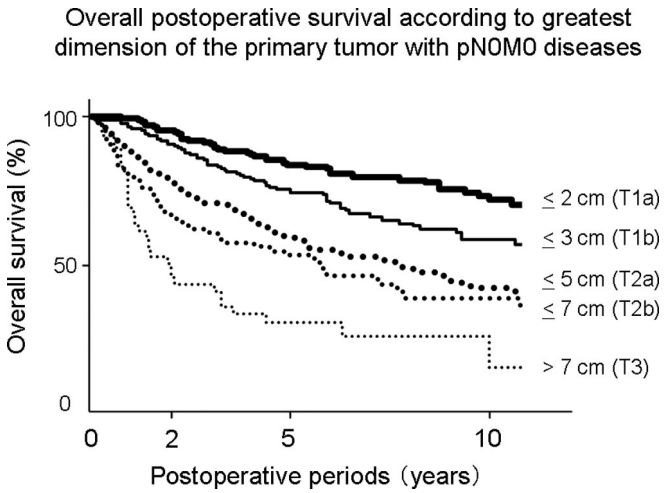

FIGURE 2. T1a ($n = 246$) versus T1b ($n = 237$), $p = 0.004$; T1b versus T2a ($n = 283$), $p < 0.001$; T2a versus T2b ($n = 95$), $p = 0.181$; and T2b versus T3 ($n = 50$), $p = 0.016$.

TABLE 1. Incidence of Invasive Growth within the Primary Tumor in Reference to the Greatest Dimension

Greatest Dimension of Primary Tumor	No. of Cases	Rate of Positive Cases: Lymphatic Permeation (%)	Vascular Invasion (%)	Pleural Invasion (%)
≤2 cm (T1a)	168	12.5	17.8	18.1[a]
2 cm ~ ≤3 cm (T1b)	169	17.2[b]	24.9[a]	29.4[a,c]
3 cm ~ ≤5 cm (T2a)	205	29.8[b]	35.3[a]	49.3[c]
5 cm ~ ≤7 cm (T2b)	48	35.4	54.2[a]	47.3[c]
>7 cm (T3)	31	32.2	64.5	87.5[c]

[a] $p < 0.05$.
[b] $p < 0.01$.
[c] $p < 0.001$.

32.3% for T3 (T1b versus T2a, $p < 0.01$). The incidence of vascular invasion within the primary tumor was 17.8% for T1a, 24.9% for T1b, 35.3% for T2a, 54.2% for T2b, and 64.5% for T3 (T1b versus T2a and T2a versus T2b, $p < 0.05$). On the other hand, the incidence of pleural invasion of the primary tumor was 18.1% for T1a, 29.4% for T1b, 49.3% for T2a, 47.3% for T2b, and 87.5% for T3 (T1a versus T1b, $p < 0.05$; T1b versus T2a and T2b versus T3, $p < 0.001$). Significant differences were observed among the newly revised T subsets in at least one incidence of lymphatic permeation, vascular invasion, or pleural invasion.

Regarding the 432 cases limited to pN0 status (Table 2), significant differences were also observed among the T subsets in at least one incidence of lymphatic permeation (T1a versus T1b, $p < 0.05$), vascular invasion (T2a versus T2b, $p < 0.05$), or pleural invasion (T1b versus T2a, $p < 0.001$; T2b versus T3, $p < 0.05$).

DISCUSSION

This study examined the relationship between the cutoff points of the tumor size for the new T category and the pathologic tumor invasiveness including intratumoral vessel invasion and pleural invasion of surgically resected NSCLC. Among the five tumor-size categories, significant differences were recognized at least in one incidence of lymphatic permeation, vascular invasion, or pleural invasion, when both cases with any pN status and only those with pN0 status were analyzed. Therefore, the newly revised T classification, which is based mainly on the tumor dimension, is considered both effective and appropriate for the clinicopathological findings of the primary tumor.

TABLE 2. Incidence of Invasive Growth within the Primary Tumor in Reference to the Greatest Dimension with pN0M0 Disease

Greatest Dimension of Primary Tumor	No. of Cases	Rate of Positive Cases: Lymphatic Permeation (%)	Vascular Invasion (%)	Pleural Invasion (%)
≤2 cm (T1a)	132	4.5[a]	12.0	16.7
2 cm ~ ≤3 cm (T1b)	125	12.0[a]	14.4	20.6[b]
3 cm ~ ≤5 cm (T2a)	126	16.7	24.2[a]	44.8[b]
5 cm ~ ≤7 cm (T2b)	29	24.1	44.8[a]	48.6[a]
>7 cm (T3)	20	20.0	55.0	84.2[a]

[a] $p < 0.05$.
[b] $p < 0.001$.

The forthcoming revision of the TNM classification has been determined and validated based on the overall survival data from a large international database.[3] However, the overall survival is affected by the differences of both the population (ethnicity, gender, age, histologic types, etc.) and treatment modality among the countries. For example, in Asian countries, NSCLC in never smokers has been increasing, which is characterized by female gender, adenocarcinoma histology, and better prognosis in comparison with that in both current and former smokers.[15–19] Furthermore, those patients with adenocarcinoma increasing in Asian countries are likely to be sensitive to epithelial growth factor receptor-tyrosine kinase inhibitors such as gefitinib and show a survival benefit from such treatment.[20–22] On the other hand, the survival differences between the platinum doublet regimens, i.e., cisplatin plus gemcitabine and cisplatin plus pemetrexed according to histology have been recently reported.[23] Therefore, in addition to survival validation, the TNM classification should be also validated from the aspect of pathologic tumor invasiveness, using surgical specimens.

Microscopic characterizations of tumor invasiveness or malignant potential at the primary tumor site include intratumoral lymphatic and vascular vessel invasion and pleural invasion. Of those, pleural invasion (p2 or more) has been conventionally used in the determination of TNM classification.[1,14] Between the tumors of 3 cm or smaller (conventional T1) and those of larger than 3 cm (conventional T2), the incidences of all the aforementioned microscopic indicators of tumor invasiveness were significantly different in the analysis of the cases with any pN status (Table 1). Therefore, the conventionally used cutoff point of 3 cm between T1 and T2 was confirmed to be very effective and appropriate for the

whole TNM system. In the analysis limited to pN0 cases, a significant difference in the incidence of lymphatic permeation between the new T1a and T1b was interestingly found to coincide with that in postoperative survival. Thus, it is suggested that the therapeutic strategy of T1a disease and T1b disease, especially the application of postoperative adjuvant chemotherapy, might thus be different, even though both diseases are still classified as the same stage IA disease.

On the other hand, a significant difference was seen in the vascular invasion between the tumors measuring 5 cm or smaller (new T2a) and those of larger than 5 cm (new T2b) in the analysis of both any type of pN cases and that limited to pN0 cases. Although the difference in the overall survival between those two tumors with a pN0 status was not statistically significant, probably due to being statistically underpowered, the newly proposed division of T2 disease is nevertheless considered to be appropriate.

In conclusion, the newly revised T classification, which is mainly based on the dimensions of the tumor, is considered to be both effective and appropriate for determining the pathologic invasiveness of the primary tumor.

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